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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,448	02/05/2002	David J. Emanuel	OC01392K	7394

24265 7590 10/05/2004

SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530

EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,448	EMANUEL ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/16/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-25 are pending and examined on the merits.

Claim Objections

2. Claim 24 is objected to because of the following informalities: The claim consists of two separate sentences. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claim 1 recites "anthracycline composition in association with a growth factor receptor inhibitor". It is unclear if the phrase "in association with" encompassed anthracycline composition which are physically associated with the inhibitor of the growth factor receptor, or if the phrase limits the administration of the anthracycline composition and the administration of the growth factor receptor inhibitor to be administered during the same course of treatment. For purpose of examination, both alternatives will be considered.

(B) The recitation of "a growth factor receptor" lacks antecedent basis in claim 6 because claim 6 specifies erbB-2, not "a growth factor receptor" which is a genus not encompassed by claim 6.

(C) The recitation of "pegylated" in claim 15 lacks antecedent basis in claim 11

(D) The recitation of "pegylated" and "doxorubicin" in claim 24 lacks antecedent basis in claim 11.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Hudziak et al (US 5,770,195) or Schwall et al (US 5,686,292).

Claim 1 is drawn to a method of treating a proliferative disease in a pateint in need of such treatment, comprising administering to said patient a therapetuically effective amount of a combination of a liposomal anthracycline composition in association with a growth factor receptor.

Hudziak et al disclose a method for treating a pateint having tumor cells which over express Her2 receptor comprising administering to said patient an antibody which binds to the Her2 receptor and administering a chemotherapeutic drug (claim 36). Hudziak et al disclose that antibodies which inhibit growth factor receptor function sensitize the tumor cells to the effect of the cytotoxic agent (abstract and claim 14). Hudziak et al disclose doxorubicin as a specific embodiment of the cytotoxic agent (claim 24), thus fulfilling the specific embodiment of claim 1 specifying an anthracycline composition. Hudziak et al disclose the specific embodiment of a method allowing for the delivery of a large amount of cytotoxic drug to the correct cell type comprising administering liposomes filled with the cytotoxic agent and coated with antibodies specifically binding to the growth factor receptor (column 10, lines 42-46).

Schwall et al disclose a method for treating a mammal having cancer comprising administering to said mammal diagnosed as having cancer an effective amount of a HGF receptor antagonist in combination with other anti-cancer agents (column 4, lines 35-41).

Schwall et al disclose doxorubicin as a specific embodiment of an anti-cancer agent (column 13, lines 38-50). Schwall et al disclose that the antagonist can be administered sequentially or concurrently with the one or more therapeutic agents (column 13, lines 49-50) and that pharmaceutical carriers comprising sustained release preparations such as liposomes, are part of the invention (column 13, lines 4-8). Thus, it is reasonable to conclude if both the antagonist and the therapeutic agent are administered concurrently that both that anti-cancer agent and the HGF receptor antagonist will be incorporated into the lysosomes, thus fulfilling the embodiment of claim 1 specifying a liposomal anthracycline composition.

7. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Cohen et al (WO 02/053596, priority to January 5, 2001)

Cohen et al disclose a method for treating cancer in a human comprising administering an antibody or antigen-binding portion thereof that specifically binds to Insulin-like Growth Factor Receptor and further comprising the administration of a chemotherapeutic agent (claims 24 and 26). Cohen et al specifically disclose the combination of an anti-IGF1 receptor antibody in combination with adriamycin (pages 6 and 7, description of Figures 9 and 10). Cohen et al disclose that the composition of the invention may be in the form of a liposome or other ordered structure suitable to high drug concentration (page 57, lines 25-27). One of skill in the art would reasonable conclude that the adriamycin would be included within said liposome, as the term "high drug concentration" would apply to the adriamycin.

8. Claims 1, 2, 4, 6, 12, 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Waksal et al (US 2002/0012663 A1, priority to August 13, 1999) as evidenced by Mendelsohn et al (US 4,943,533) and Physicians Desk Reference On-Line Edition (PDR) 2004.

The specific embodiments of claim 1 are set forth above. Claim 2 embodies the method of claim 1, wherein said growth factor inhibitor is an antibody directed against the extracellular domain of a growth factor receptor, wherein said patient is a treatment experienced pateint having a proliferative disease and/or has at least one cardiac risk factor and/or has had previous anthracycline therapy. Claim 4 embodies the method of claim 2 wherein the liposomal anthracycline is pegylated liposomal doxorubicin comprising PEG-derivatized disteroyl

phosphatidylehtnaolamine, hydrogenated soy phosphatidylcholine and cholesterol. Claim 6 embodies the method of claim 4 wherein the antibody is a monoclonal antibody which binds to the extracellular domain of erbB2 expressed on human malignant cancer cells. Claim 12 embodies the method of claim 6 wherein the proliferative disease is breast cancer, lung cancer, pancreatic cancer, colon cancer, myeloid leukemia, melanoma, thyroid follicular cancer, bladder carcinoma, glioma, myelodysplastic syndrome, ovarian cancer or prostate cancer. Claim 18 embodies the method of claim 4 wherein the proliferative disease us an epithelial cancer.

Waksal et al disclose a method of inhibiting the growth of refractory tumour that are stimulated by a ligand of EGF receptor in human patients, comprising treating said pateint with an effective amount of an EGF/HER1 antagonist and a chemotherapeutic agent (claim 22). Waksal et al disclose the method wherein the antibody 225 binds to the EGF receptor. Mendelsohn et al disclose that the 225 antibody competes with EGF for binding to the EGF receptor, thus, it is reasonable to conclude that the 225 antibody binds to the extracellular portion of the EGF receptor. Waksal et al disclose doxorubicin lipo (doxil) and daunorubicin lipo as a preferred embodiment of a chemotherapeutic agent (page 6, paragraph 0087 and claim 30), thus fulfilling the specific embodiment of claim 1 specifying a liposomal anthracycline. The 2004 PDR discloses the chemical constituents of doxil including the limitations of claim 2 (page 2, lines 3-7). Waksal et al disclose the treatment of tumors of the breast, lung, pancreas, colon, bladder, ovary, prostate and brain (claim 32), fulfilling the specific embodiments of claims 12 and 18. Waksal et al disclose that the refractory tumor had been previously treated by chemotherapy. The reference does not specifically teach that the prior chemotherapy consisted of a anthracycline treatment. However, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art method does not encompass the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from that taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 2, 4, 6, 8, 9, 10, 12, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waksal et al (US 2002/0012663 A1) in view of Kastrup et al, Editor (Drug Facts and Comparisons, 1999, pp. 3447-3455) and Parahadadiopoulos et al (PNAS, 1991, Vol. 88, pp. 11460-11464, reference of the IDS filed April 16, 2003).

Claim 8 embodies the method of claim 6 wherein the pegylated liposomal anthracycline composition and the antibody are administered together. Claim 9 embodies the method of claim 6 wherein the liposomal anthracycline composition is administered first. Claim 19 embodies the method of claim 4 wherein the pegylated anthracycline composition is administered in the amount of about 20 mg/m2 to about 50 mg/m2 over a period of about 45 minutes, every three to four weeks.

Waksal et al teach a method of inhibiting the growth of refractory tumour that are stimulated by a ligand of EGF receptor in human patients, comprising treating said pateint with an effective amount of an EGF/HER1 antagonist and a chemotherapeutic agent (claim 22). Waksal et al teach doxorubicin lipo (doxil) and daunorubicin lipo as a preferred embodiment of a

chemotherapeutic agent (page 6, paragraph 0087 and claim 30), thus fulfilling the specific embodiment of claim 1 specifying a liposomal anthracycline. Waksal et al teach the method wherein the antibody 225 binds to the EGF receptor. Mendelsohn et al teach that the 225 antibody competes with EGF for binding to the EGF receptor, thus, it is reasonable to conclude that the 225 antibody binds to the extracellular portion of the EGF receptor. Waksal et al teach doxorubicin lipo (doxil) and daunorubicin lipo as a preferred embodiment of a chemotherapeutic agent (page 6, paragraph 0087 and claim 30), thus fulfilling the specific embodiment of claim 1 specifying a liposomal anthracycline. The 2004 PDR discloses the chemical constituents of doxil including the limitations of claim 2 (page 2, lines 3-7). Waksal et al teach the treatment of tumors of the breast, lung, pancreas, colon, bladder, ovary, prostate and brain (claim 32), fulfilling the specific embodiments of claims 12 and 18. Waksal et al teach that the refractory tumor had been previously treated by chemotherapy. Waksal et al teach examples of said refractory tumors include carcinomas, gliomas and tumors of the breast, lung, pancreas, colon and prostate (page 2, paragraph 0031), thus fulfilling the specific embodiments of claims 12 and 18.

Kastrup et al (Drug Facts and Comparisons, 1999, pp. 3447-3455) teach that special attention must be given to cardiac toxicity in patients who have received total doses of doxorubicin exceeding the recommended amount of 550 mg/m2 and that dose-related incidents range to 20% for patients receiving doses of doxorubicin of greater than 700 mg/m2, and that the limit for patients receiving radiotherapy to the mediastinal area, or other potentially cardiotoxic agents such as cyclophosphamide or daunorubicin, may be lower (page 3448, lines 10-17, under "Warnings"). Kastrup et al teach that because of the slower clearance of doxil relative to free doxorubicin, the AUC of liposomal doxorubicin is two to three orders of magnitude larger than the AUC for a similar dose of free doxorubicin (page 3448, lines 4-9 under the heading "Doxorubicin HCL (ADR)"). Kastrup et al teach a recommended dose of 20 mg/m2 of doxorubicin in lipsomal formulation over 30 minutes, once every three weeks which fulfills the specific embodiment of claim 19.

Parahadadiopoulos et al teach sterically stabilized liposomes included in the formulation of PEG-liposomes exhibit prolonged circulation time in blood and clearance rates that are completely dependent of dosage over a wide range (page 11460, second column, lines 6-10).

Parahadadiopoulos et al teach that said liposomes produce a marked enhancement of antitumor activity of encapsulated doxorubicin and epirubicin in mice against both lymphoma and colon carcinoma cells, with a concomitant decrease in toxicity (page 11460, first column, lines 10-14). Parahadadiopoulos et al teach the sterically stabilizes liposomes have a therapeutic index which is much higher than that observed with conventional liposomes (page 11460, first column, lines 14-16). Parahadadiopoulos et al teach that marked decrease in accumulation in the liver and spleen and a marked increase in accumulation in tumors (abstract, lines 9-11). Parahadadiopoulos et al teach the composition of liposomes made from polyethylene glycol conjugated to disteroyl phosphatidyl ethanolamine, hydrogenated soy phosphatidyl choline, cholesterol and alpha tocopherol in molar ratio which is the same as the weight ratios of claims 5 and 6 (page 11461, first column, lines 18-24). Parahadadiopoulos et al teach that the lower acute toxicity of the anthracycline-loaded PEG-liposomes is due to the delayed clearance of the drug from the blood and the reduction of peak plasma levels of the free drug which adversely affects sensitive non-target tissues such as the heart (page 11464, first column, lines 18-22).

It would have been prima facie obvious at the time the invention was made to administer the anti-EGF antibody in combination with the doxil in the dosage taught by Kastrup et al. One of skill in the art would have been motivated to do so by the teachings of Kastrup et al identifying cardiac risk factors for patients undergoing treatment with doxorubicin or other chemotherapeutic agent which causes cardiac toxicity or radiation to the mediastinal area and the teachings of Parahadadiopoulos et al on the increased therapeutic index attributed to Pegylated liposomes comprising doxorubicin and the decrease in the peak plasma levels afforded by administration of said liposomes which lead to decreased cardio-toxicity. One of skill in the art would be motivated to use the pegylated liposomes comprising doxorubicin in place of the free drug in order to avoid the cardiac toxicity associated with the cumulative administration of said free drug; one of skill in the art can ascertain from the teachings of Kastrup et al that the higher therapeutic index of doxil allows for a dose of 20 mg/m2 versus the 60-75 mg/m2 of free doxorubicin (Kastrup et al, page 3450, lines 1-2 under "conventional doxorubicin" and lines 1-3 under "Liposomal doxorubicin"). Thus, one of skill in the art would be motivated to use liposomal doxorubicin in place of free doxorubicin in order to prevent cardiac toxicity in treatment experience patients.

12. Claims 1–9 and 11-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albanell and Baseiga, (Drugs of Today, 1999, Vol. 35, pp. 931-946, reference of the IDS submitted April 16, 2003) in view of Kastrup et al, Editor (Drug Facts and Comparisons, 1999, pp. 3447-3455) and Parahadadiopoulos et al (PNAS, 1991, Vol. 88, pp. 11460-11464).

The specific embodiments of claims 1, 2, 4, 6, 8, 9, 10, 12, 18 and 19 are set forth above. Claim 3 embodies the method of claim 2 further comprising an additional antineoplastic agent. Claim 5 embodies the method of claim 3 wherein the liposomal anthracycline is pegylated liposomal doxorubicin comprising PEG-derivatized disteroyl phosphatidylehtnaolamine, hydrogenated soy phosphatidylcholine and cholesterol.. Claim 7 embodies the method of claim 4 wherein the antibody is a monoclonal antibody directed against the extracellular domain of an erbB-2 tyrosine kinase receptor expressed on the surface of human malignant cancer cells. Claim 11 embodies the method of claim 3 wherein the antibody is trastuzusamab. Claim 13 embodies the method of claim 11, wherein the proliferative disease is breast cancer, lung cancer, pancreatic cancer, colon cancer, myeloid leukemia, melanoma, thyroid follicular cancer, bladder carcinoma, glioma, myelodysplastic syndrome, ovarian cancer or prostate cancer. Claim 14 embodies the method of claim 11 wherein the additional antineoplastic agent is selected from the group consisting of uracil mustard, cyclophosphamide, ifosamide, melphalan, chlorambucil, temozolomide, 5-FU, fludarabine phosphate, Gemcitabine, Paclitaxel, Docetaxel, Interferons, Etoposide, Tamoxifen, Leuprolide, Flutamide, Toremifene, cisplatin, Carboplatin, Navelbene, CPT-11, anastrazole, Letrazole and Capecitabine. Claim 15 embodies the method of claim 11 wherein the pegylated liposomal composition, the antibody directed against the extracellular domain of the growth factor receptor and the additional antineoplastic agent are administered sequentially. Claim 16 embodies the method of claim 11 wherein the additional antineoplastic agent is cyclophosphamide. Claim 17 embodies the method of claim 15, wherein the proliferative disease is breast cancer, lung cancer, pancreatic cancer, colon cancer, myeloid leukemia, melanoma, thyroid follicular cancer, bladder carcinoma, glioma, myelodysplastic syndrome, ovarian cancer or prostate cancer. Claim 20 embodies the method of claim 4 wherein the antibody directed at the extracellular domain of the growth factor receptor is administered first in the amount of about 2 to about 6 mg/kg given once over a time period of about 60 to

about 90 minutes and subsequently administered in the amount of about 2 to 6 mg/kg given over a period of about 60 to 90 minutes every one to four weeks. Claim 21 embodies the method of claim 5 wherein the additional antineoplastic agent is administered in the amount of about 400 to about 600 mg/m2 given over a period of about 20 to about 60 minutes every two to four weeks. Claim 22 embodies the method of claim 5 wherein the antibody is trastuzusamab. Claim 23 embodies the method of claim 5 wherein the additional antineoplastic agent is cyclophosphamide. Claim 24 embodies the method of claim 5 wherein the pegylated liposomal doxorubicin composition is administered in the amount of about 20 to about 50 mg/m2 given over a period of about 45 minutes to about 90 minutes every three to four weeks; trastuzusamab is administered first in the amount of about 2 to about 8 mg/kg given over a period of about 60 to about 90 minutes and subsequently administered in the amount of about 2 to about 8 mg/kg given over a period of about 60 to about 90 minutes every one to four weeks, and the additional antineoplastic agent is cyclophosphamide and is administered in the amount of about 400 to about 600 mg/m2 given over a period of about 20 to about 60 minutes every two to four weeks.

Albanell and Baseiga teach a method of treating breast cancer comprising the administration of the combination of doxorubicin and cyclophosphamide to patients not previously treated with doxorubicin, on a schedule of 60 mg/m2 doxorubicin plus 600 mg/m2 cyclophosphamide (page 941, second column, lines 6-7). Albanell and Baseiga teach that all chemotherapy regimens were administered once every three weeks (page 941, second column, lines 11-14). Albanell and Baseiga teach that half of the patients were then selected to receive Albanell and Baseiga in an initial 4 mg/kg loading followed by 2 mg/kg every week (page 941, second column, lines 15-19). Albanell and Baseiga teach that myocardial dysfunction syndrome was more common in the combined treatment of doxorubicin, cyclophosphamide and trastuzusamab than with doxorubicin combined with cyclophosphamide (page 941, second column, lines 24-27). Thus, Albanell and Baseiga teach the specific embodiments of all the instant claims with the exception of the administration of liposomal doxorubicin rather than doxorubicin, the treatment of a patient with a cardiac risk factor or previous anthracycline therapy, the specific embodiments of claims 4 and 5, and the amount and time of administration of the pegylated anthracyclin in claims 19 and 24.

Kastrup et al (Drug Facts and Comparisons, 1999, pp. 3447-3455) teach that special attention must be given to cardiac toxicity in patients who have received total doses of doxorubicin exceeding the recommended amount of 550 mg/m2 and that dose-related incidents range to 20% for patients receiving doses of doxorubicin of greater than 700 mg/m2, and that the limit for patients receiving radiotherapy to the mediastinal area, or other potentially cardiotoxic agents such as cyclophosphamide or daunorubicin, may be lower (page 3448, lines 10-17, under "Warnings"). Kastrup et al teach that because of the slower clearance of doxil relative to free doxorubicin, the AUC of liposomal doxorubicin is two to three orders of magnitude larger than the AUC for a similar dose of free doxorubicin (page 3448, lines 4-9 under the heading "Doxorubicin HCL (ADR)"). Kastrup et al teach a recommended dose of 20 mg/m2 of doxorubicin in lipsomal formulation over 30 minutes, once every three weeks which fulfills the specific embodiment of claim 19.

Parahadadiopoulos et al teach sterically stabilized liposomes included in the formulation of PEG-liposomes exhibit prolonged circulation time in blood and clearance rates that are completely dependent of dosage over a wide range (page 11460, second column, lines 6-10). Parahadadiopoulos et al teach that said liposomes produce a marked enhancement of antitumor activity of encapsulated doxorubicin and epirubicin in mice against both lymphoma and colon carcinoma cells, with a concomitant decrease in toxicity (page 11460, first column, lines 10-14). Parahadadiopoulos et al teach the sterically stabilizes liposomes have a therapeutic index which is much higher than that observed with conventional liposomes (page 11460, first column, lines 14-16). Parahadadiopoulos et al teach that marked decrease in accumulation in the liver and spleen and a marked increase in accumulation in tumors (abstract, lines 9-11). Parahadadiopoulos et al teach the composition of liposomes made from polyethylene glycol conjugated to disteroyl phosphatidyl ethanolamine, hydrogenated soy phosphatidyl choline, cholesterol and alpha tocopherol in molar ratio which is the same as the weight ratios of claims 5 and 6 (page 11461, first column, lines 18-24). Parahadadiopoulos et al teach that the lower acute toxicity of the anthracycline-loaded PEG-liposomes is due to the delayed clearance of the drug from the blood and the reduction of peak plasma levels of the free drug which adversely affects sensitive non-target tissues such as the heart (page 11464, first column, lines 18-22).

It would have been prima facie obvious at the time the claimed invention was made to substitute an administration of 20 mg/m2 of doxorubicin in lipsomal formulation over 30 minutes, once every three weeks for the administration of 60 mg/m2 doxorubicin given once every three weeks in the combination chemotherapy as taught by Albanell and Baseiga. One of skill in the art would have been motivated to do so by the teachings of Albanell and Baseiga on the increased incidence of myocardial dysfunction observed in the combination therapy with doxorubicin, cyclophosphamide and trastuzusamab relative to the incidence of myocardial dysfunction observed in the combination of doxorubicin and cyclophosphamide without trastuzusamab and the teachings of Parahadadiopoulos et al on the lower acute toxicity of anthracyclin-loaded PEG liposomes due to the reduction of peak plasma levels which reduces the adverse effects on non-target tissues such as the heart, and the teachings of Kastrup et al on the increased therapeutic index of liposomal doxorubicin which is evident from the lower recommended dose relative to conventional doxorubicin (20 mg/m2 versus 60-75mg/m2, page 3450, "Administration and Dosage"). One of skill in the art would reasonably conclude that the combination of doxorubicin, cyclophosphamide and trastuzusamab is in of itself a cardiac risk factor. Further one of skill in the art would be motivated to decrease the risk of myocardial dysfunction both in patients previously exposed to anthracyclines and other chemotherapeutic agent s which cause cardio toxicity and in patients who have not received previous chemotherapy by lowering the total amount of doxorubicin which is administered (20mg/m2 versus 60mg/m2).

13. Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albanell and Baseiga, (Drugs of Today, 1999, Vol. 35, pp. 931-946) and Kastrup et al, Editor (Drug Facts and Comparisons, 1999, pp. 3447-3455) and Parahadadiopoulos et al (PNAS, 1991, Vol. 88, pp. 11460-11464) as applied to claims 1-9 and 11-24 above, and further in view of Waksal et al (US 2002/0012663) and the abstract of Hudis et al (J. Clin. Oncol., Jan 1999, Vol. 17, pp. 93-100).

Claim 10 embodies the method of claim 6 wherein the antibody directed against the extracellular domain is administered first. Claim 25 embodies the method of claim 24 wherein the pegylated liposomal doxorubicin composition is administered first followed by cyclophosphamide and the trastuzusamab. Albanell and Baseiga teach a method wherein doxorubicin is administered together with cyclophosphamide followed by trastuzusamab. None

of the aforesaid references teaches the administration of doxorubicin followed by cyclophosphamide, or the administration of trastuzusamab before the administration of the liposomal doxorubicin.

Waksal et al teach the administration of the EGFR/HER2 antibody before treatment with chemotherapeutic agents (page 7, paragraph 0095, lines 6-10).

The abstract of Hudis et al teaches a chemotherapeutic regimen comprising the administration of cyclophosphamide after the administration of doxorubicin.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to optimize the treatment protocol by changing parameters known to be variable, such as the order of administration of drugs within a combination regimen. One of skill in the art would have been motivated to do so by the teachings of Waksal et al that the anti-HER2 antibody is administered before the chemotherapeutic agent and the teachings of the abstract of Hudis et al which demonstrates that cyclophosphamide need not be co-administered in the same infusion with doxorubicin.

Conclusion

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Kozlowski et al (US 6,337,338) and Boyle et al, (Cancer Research, 1997, Vol. 57, pp. 2404-2409).

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
8/30/2004

Karen A. Canella
KAREN A. CANELLA PH.D
PRIMARY EXAMINER